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Name of Candidate: **Nadine S. Bekkouche**, Master of Science in Medical and Clinical Psychology,

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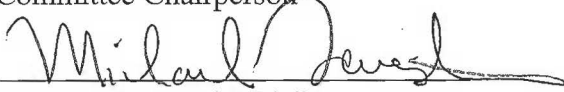
THESIS AND ABSTRACT APPROVED:

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David S. Krantz, Ph.D.

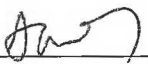
6/6/11

DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY  
Committee Chairperson

  
\_\_\_\_\_  
Michael Feuerstein, Ph.D.

6/7/11

DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY  
Thesis Advisor

  
\_\_\_\_\_  
Andrew Waters, Ph.D.

6/6/11

DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY  
Committee Member

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Nadine S. Bekkouche  
Department of Medical and Clinical Psychology  
Uniformed Services University

Abstract

Title of Thesis: The Neuromatrix Theory of Pain and Angina during Exercise

Stress Testing: Results from the PIMI Study

Nadine S. Bekkouche, Master of Science, 2011

Thesis directed by: David S. Krantz, Ph.D.

Professor and Chairman

Department of Medical and Clinical Psychology

Background: The Neuromatrix Theory of pain (Melzack, 1999) describes five factors (cognitive-sensory, affective-emotional, nociception, inhibitory, and CNS modulation) that operate to modulate pain. This study assesses the interplay among these factors in the development of exercise-induced anginal pain. Methods: Participants were 175 patients (26 women) with documented CAD and a positive bicycle exercise stress test from the National Heart, Lung, and Blood Institute (NHLBI) Psychophysiological Investigations of Myocardial Ischemia (PIMI) study. Of these, 62 patients reported angina during testing. Patients completed the Rose Angina Questionnaire (cognitive-sensory measure), the Beck Depression Inventory (affective-emotional measure), a thermal pain threshold test (nociception), the modified Autonomic Perception Questionnaire (symptom perception/inhibition measure). Plasma  $\beta$ -endorphin levels (opioid modulation) were also assessed at rest and at peak exercise stress. We assessed main effects and interactions among the five factors. Results: Logistic regression examining the five factors of the Neuromatrix model revealed that only history of angina predicted exercise-induced angina (OR=8.59, 95% CI=4.00-18.48) when adjusting for

age, sex, history of diabetes, history of hypertension, history of myocardial infarction and maximum ST-segment depression during ischemia. Without adjusting for covariates, depressive symptoms marginally predicted exercise-angina ( $p=0.097$ ,  $OR=1.05$ , 95%  $CI=0.99-1.11$ ). The five factors as a block were predictive of exercise-angina ( $p<0.001$ ) adjusting for covariates. In this model, only history of angina ( $OR=7.10$ , 95%  $CI=3.09-16.30$ ) was independently predictive of angina. The interaction of depressive symptoms and hot pain threshold was marginally significant ( $p=0.054$ ) such that exercise-angina was more prevalent in individuals with lower pain thresholds and more depressive symptoms. Conclusion: History of angina predicts exercise-angina in an acute situation. There may be interactions among factors such that depressive symptoms are predictive in individuals with a lower pain threshold.

THE NEUROMATRIX THEORY  
OF PAIN AND ANGINA DURING  
EXERCISE-STRESS TESTING:  
RESULTS FROM THE PIMI STUDY

by

Nadine Samia Bekkouche

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## **Introduction**

Coronary artery disease (CAD) is the leading cause of death in the United States of America (American Heart Association, 2010). One of the most common clinical manifestations of CAD is that of angina pectoris, defined as chest pain due to CAD. Angina pectoris is often one of the earliest signs of CAD and carries important prognostic significance. However, though prevalent, angina does not reliably follow coronary artery occlusions or events. Indeed, as many as half of first myocardial infarction (MI), defined as necrosis of myocardial tissue due to insufficient oxygen supply, may be asymptomatic (Kannel & Abbott, 1984). Milder CAD events, such as myocardial ischemia, defined as the imbalance between the myocardial oxygen supply and demand, show an even greater proportion of symptomless events, around 60-80% (Deanfield, Shea, & Selwyn, 1985; Singh, Nademanee, Figueras, & Josephson, 1986; Maseri, Chierchia, & L'Abbate, 1980). The absence of pain in cases of coronary events is a dangerous clinical problem (Gutterman, 2009; Ditto, Lavoie, Campbell, Gordon, Arsenault, & Bacon, 2010; Hermann et al., 2010).

The occurrence of a clinical coronary event such as myocardial ischemia without pain is termed 'silent ischemia'. The danger of silent ischemia is that the pain associated with ischemia serves as a warning signal to the individual to seek help or stop what they are doing (Ditto et al., 2010). There is a dilemma in the area of anginal pain. While chronic episodic angina creates an impairment in quality of life as well as the psychological and behavioral sequelae of chronic pain, the absence of this episodic pain creates a situation where an individual can be living with a chronic disease with no signal to slow down or seek help.

While considerable research in the past few decades has been aimed at determining the psychological and physiological causes of silent versus symptomatic ischemia (Stern, 1998) the mechanisms and predictors of this syndrome remain unclear. As with many complex pain problems, acute, episodic, and chronic, the answer might be multidimensional (Taylor, Stotts, Humphreys, Treadwell, & Miaskowski, 2010; O'Sullivan, Beales, Jensen, Murray, & Myers, 2011). However the current literature focuses on unidimensional factors in angina. Multidimensional models of pain might help explain this pain syndrome and provide valuable clues to improving treatment.

One such multidimensional model that has been used to explain other acute and chronic pain syndromes is the Neuromatrix Theory (NMT; Melzack, 1993, 1999, 2001; described below). This study applies the NMT of pain, which conceptualizes pain as an experience predicted by several factors and by the interactions among them, to the study of silent versus symptomatic ischemia. The background of this paper is divided into 6 sections. The first section describes the NMT and how it applies to the experience of anginal pain. The second section reviews the mechanisms and physiological causes of anginal pain. The third section describes the influence of psychological distress in particular depression, on anginal pain. The fourth section reviews the research on the five components of the NMT as they apply to anginal pain. The fifth section describes how these factors are expected to interact to predict anginal pain. The sixth and final section serves as an introduction to the study's specific aims and hypotheses.

### **Neuromatrix Theory of Pain**

The study and conceptualization of pain has undergone many shifts over the past 200 years. Historically, pain was thought to be directly related to a sensory experience or

physical injury (as cited in Melzack 1993). However, Specificity Theory could not explain many of the problems of pain syndromes, such as how a person might fail to experience pain despite the presence of nociceptive input, such as in silent ischemia, or how a person may experience pain in the absence of any observable nociceptive input, such as in Syndrome X.

Given these limitations, Specificity Theory was replaced by a theory that could incorporate multiple determinants of pain, the Gate-Control Theory (Melzack & Wall, 1965). Gate-Control Theory became the dominant theory of pain in the past century by postulating that the experience of pain is a combination of sensory inputs and central modulating inputs, including psychological factors. The dorsal horns of the spinal cord were proposed as the site of processing of these different inputs. The importance and impact of the Gate-Control Theory is reflected in the definition of pain put forth by the International Association for the Study of Pain (IASP) as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage or is described in terms of such damage” (IASP, 1986).

More recently, Gate-Control Theory has been modified and extended into the NMT of pain (Melzack, 1993, 1999). The NMT proposes that the experience of pain is triggered by the interplay of five factors that provide inputs to and modulation of the pain experience. These include 1) nociceptive sensory inputs (visceral, cutaneous or somatic); 2) the non-nociceptive sensory inputs, such as vision, that contribute to the cognitive interpretation of the experience; 3) state and trait emotional and cognitive factors modulated by other areas of the brain; 4) neural inhibition which is present in the CNS, which endeavors to dampen any extreme sensory experience; and 5) the body's stress systems, which include the autonomic, as well as endocrine, immune, and opioid systems

(Melzack, 1999). According to the NMT, these five factors can operate either singly or in combination to evoke pain.

This theory conceptualizes pain as an experience that can be generated in the brain even in the absence of any peripheral nociceptive input. In other words, the pain experience of angina is codified in the brain with a particular “pain signature”, and thus can be generated without peripheral stimulation or nociception. This “pain signature” is then what is processed in the parts of the cortex responsible for conscious experience. Therefore, any of the five factors described above can modulate the pain signature in the brain and pain expression and behavior (Melzack, 1993). In patients with a history of angina pectoris, the “pain signature” for ischemic pain would be more easily triggered because of its repeated occurrence. Since this pain signature would exist as widely distributed in the brain, other factors that have a wide CNS distribution may easily affect this pain signature. Examples of these other factors would include depression or opioid modulation, which seem to be powerful modulators of a pain experience such as angina (IASP, 2004; American Academy of Pain Medicine, 2004; Sheps, Hinderliter, Bragdon, Adams, Herbst, & Koch, 1988).

This theoretical framework provides the basis for conceptualizing pain as multidimensional and is of particular value when conceptualizing syndromes that lack a one-to-one relationship between nociceptive input and pain perception, such as anginal pain during ischemia. Though initially conceptualized to describe chronic pain syndromes, the NMT may provide valuable insights to the triggers of a recurring episodic pain syndrome like angina. The following sections aim at discussing what is known

about anginal chest pain and how its study might benefit from the application of the NMT.

### **Anginal Pain**

Previously, it was thought that myocardial ischemia, or the inadequate supply of oxygen to the heart muscle, always provoked chest pain, and thus individuals with angina pectoris (pain in the chest) were the only ones considered to be at risk from heart disease (Stern, 1998). However, in the past 40 years, it has become clear that myocardial ischemia in fact most often does not provoke chest pain.

Specificity Theory would suggest that these results can be explained in that the cases of myocardial ischemia that do not provoke pain simply are not severe enough to reach pain threshold. In other words, that acute anginal pain will reliably follow if nociceptive stimulation passes a certain threshold. Indeed, ischemic severity seems to be important in provoking anginal pain. For example, ischemia from smoking or mental stress is much less likely to cause pain than ischemia from exercise (Deanfield et al., 1985). In stable angina pectoris, or angina relatively predictably caused by exertion, pain is often elicited after exercise, eating or strong emotion (Sylvén, 1989; Ketterer, Mahr, Cao, Hudson, Smith, & Knysz, 2004) but not after milder mental stresses (Freedman & Wong, 1998). Thus it seems that more severe ischemia does provokes pain more reliably than less severe ischemia (Marcassa, 1997).

However, severe ischemia, though necessary, is not sufficient to provoke pain (Glazier, Chierchia, Brown, & Maseri, 1986; Nihoyannopoulos, Marsonis, Joshi, Athanassopoulos, & Oakley, 1995; Marwick, 1995). Reports have shown no reliable relationship between anginal pain and ischemic severity, as long as the ischemic severity

surpasses a certain threshold (Quyyumi, Wright, Mockus, & Fox, 1985; Selwyn, Shea, Deanfield, Wilson, Horlock, & O'Brien, 1986; Carboni, Lahiri, Cashman, & Raftery, 1987). As such, the problem of angina is that the pain experience does not reliably follow myocardial ischemia, even in the same patient, even for the same degree of ischemia (Sylvén, 1989; see Figure 1).

The NMT may help explain this variation. Indeed, the interplay between affective, cognitive, and physiological factors may be what determines pain perception, as opposed to physiological nociceptive stimulation alone. For example, a person who is in a state of emotional distress may display a lower physical pain threshold. Alternatively, an individual who has higher levels of endorphins may be less likely to react to nociceptive input so strongly. A person with no increased negative cognitions around pain may also react to it less strongly. As such, the NMT may offer guidance in determining what factors affect pain perception during ischemia given its unreliable association with nociceptive input.

**Physiological mechanisms of angina.** The process by which cardiac visceral nociceptive input becomes translated into pain is quite complex. Myocardial ischemia occurs when there is a greater demand for oxygen to the heart than there is supplied by the blood. In most cases, this inadequate supply of blood is due to a lack of perfusion of the heart by the epicardial coronary arteries due to obstruction or vasospasm (Kumar, Abbas, & Fausto, 2005). This imbalance between oxygen supply and demand leads to a dysfunction in the conduction function of the heart, which is reflected in the electrocardiogram (ECG). These electrical changes then modify the pumping function of the heart (Sylvén, 1989).



The onset of pain occurs either during the more severe disruptions in heart pumping, or can be due to changes in the sensitivity of the coronary arteries through the accumulation of atherosclerotic plaque (Sylvén, 1989). The pain can thus begin several minutes after the start of the ischemia (Kumar et al., 2005; Gutterman, 2009). Typical anginal pain is felt as occurring below the sternum, radiating to the left arm (Sylvén, 1989).

**Silent ischemia.** There are several attempts to explain the occurrence of silent ischemia, apart from the physiological one described above. One such hypothesis is that of “neural stunning” (Gutterman, 2009). According to this approach, once a person has angina pectoris, their myocardial nerves subsequently undergo a “refractory period” where the myocardium becomes insensitive to pain. Though a less commonly cited hypothesis, it can explain why the same individual can have a symptomatic attack followed by a non-symptomatic attack for the same severity of ischemia. The problem with this hypothesis is that some patients seem to entirely lack this refractory period, whereas others do not seem to ever have experienced any pain at all.

Another, more commonly cited, hypothesis is that there is a change in the pain perception system among patients with silent ischemia that makes them less likely to perceive pain across several pain domains over time (Droste et al., 1983; Droste, Greenlee, & Roskamm, 1986; Falcone et al., 1988; Glazier et al., 1986). It is unclear exactly what the mechanism is for this change in pain sensitivity. However, support for this hypothesis is seen in that individuals with silent ischemia seem to be less likely to report pain generally, across a variety of pain triggers (Freedland, Carney, Krone, Smith, Rich, Eisenkramer, & Fischer, 1991; Falcone et al., 1988). One suggestion for the

mechanism underlying this phenomenon is that the pain system may be altered, for example, through changes in endorphin mechanism (Sheps et al., 1988), as in cases of very severe CAD where individuals no longer feel pain (Van Rijn & Rabkin, 1986; Droste et al., 1988; Glusman et al., 1996). In these individuals, the opioid reactivity would produce stronger analgesia of pain from most inputs, including the myocardium. In this sense, the pain is truly not perceived in these individuals.

A related set of hypotheses concerns personality differences between patients with silent versus symptomatic ischemia. The first of these hypotheses is that patients with silent ischemia are somehow biased against pain reporting (Davies et al., 1993) and the second, that they are lower on trait ‘symptom perception’ (i.e., the tendency to perceive bodily symptoms). In support of the first hypothesis, qualities like “masculinity” (Droste et al., 1983), “harm avoidance”, “reward dependence”, “somatic awareness”, and “depression” (Freedland et al., 1991) correlate with silent ischemia. However, it seems that these psychological traits are not reliably predictive of anginal pain. Indeed, when a number of psychological traits are factor analyzed and then the factors are used to predict anginal pain, it seems like the factor relating to a bias towards or away from symptom reporting (e.g., strong loadings of denial or novelty seeking) do not predict silent versus symptomatic ischemia (Freedland, Carney, Krone, Case, & Case, 1996). Rather, the factor related to awareness or inhibition of physical symptoms are predictive of pain perception. Thus, in support of the second hypothesis, it seems like the psychological characteristic underlying some of these associations is the tendency towards awareness or inhibition of physical symptoms.

The next section will discuss the psychological factors associated with silent ischemia in more detail. However, before moving on, it is important to emphasize that the psychological factors involved in pain perception and reporting have physiological correlates in the CNS. As such, to propose a psychological theory for silent ischemia does not indicate that the physiological ones must be wrong. Indeed, the notion that CNS modulations of pain might influence the physiological pain mechanism does not mean that these CNS differences do not have personality correlates; psychological processes have a neural basis. For example, the change in the opioid system that is proposed to occur in silent ischemia might also be expressed as a change in depressive symptoms in the same individual (Sheps et al., 1988). As such, examining the psychological correlates of pain, which is itself a psychological experience, is of particular value. The following section reviews the psychological correlates of silent versus symptomatic ischemia in more detail.

### **Psychological factors in silent versus symptomatic ischemia**

Depressive symptoms are some of the most commonly studied psychological factors associated with CAD. Approximately 20% of individuals with heart disease also suffer from depression and the incidence of depression is three times higher in CAD patients than in the general public (Rozanski, Blumenthal, & Kaplan, 1999; Kessler et al., 2003). The co-morbid diagnosis of CAD and depression seems to be related to worse prognosis. Indeed, over 10 years of follow up in patients with CAD, individuals with moderate to severe levels of depressive symptoms showed an 84% greater mortality risk compared with the individuals with the lowest levels of depression, controlling for initial disease severity and treatment (Barefoot, 1996).

Depressive symptoms are also commonly associated with recurrent episodic pain and chronic pain (Baune, Caniato, Garcia-Alcaraz, & Berger, 2008; Taylor et al., 2010). There seems to be a particular relationship between depression and cardiac symptoms (Rutledge et al., 2006). This may be in part because cardiac symptoms – in particular chest pain – is inherently anxiety-provoking and perhaps discouraging to individuals with heart problems. Indeed, chest pain is a dangerous kind of pain in the context of a chronic health problem like CAD. Its occurrence may cause worry in the short term, and depression over time.

In episodic pain like angina, the combination of the nociceptive input of chest pain and the emotional reaction to chest pain, especially in individuals diagnosed with CAD, the perceived pain might be greater. Some even suggest pain may simply be an epiphenomenon of underlying major depressive disorder or somatic disorders (Baune et al., 2008). However, as alluded to above, in some cases stress also leads to the release of opioids that blunt the perception of pain. Therefore, it is possible that in some situations, the stress of angina increases the perception of pain, whereas in others, it does not (Sheps et al., 1988). Though anxiety has been demonstrated to be strongly related to chest pain of a non-cardiac origin, depression is the more important factor in individuals with pain and documented CAD (Sheps, Creed, & Clouse, 2004).

The inherently stressful nature of chest pain in CAD, added to the physiological stress involved in exertional chest pain, may influence the relationship between depression and pain perception in an acute situation. If the past experience of disease or pain has given rise to high levels of stress that have contributed to depression, then the pain response might be greater. If the stress burden in an acute situation is increased

beyond a certain level, the pain perception might be lesser. The former view would explain research that has found that depressed patients are more likely to develop angina post-MI, suggesting a role for depression in the exacerbation of anginal pain syndromes (Arnold et al. 2009). The latter view would explain how depressive symptoms are less robust predictors of acute pain. These relationships will be discussed more fully in a section below.

Other psychological factors have been alluded to above, such as the tendency to perceive or inhibit symptoms and the tendency to interpret those symptoms in a particular way, as well as worry and anxiety. However, before discussing the impact of these factors on the experience of silent versus symptomatic ischemia, suffice it to say that the relationships between psychological factors and pain syndromes are complex and most likely operate in conjunction with physiological factors. Sections below will cover some of these key relationships in more depth.

### **Components of the Neuromatrix Theory**

As noted previously, Melzack's NMT of pain (1993) identifies five factors which directly and indirectly produce the pain experience. The following sections describe what is known about the relationship of anginal pain to these factors, namely, 1) nociceptive input, 2) cognitive interpretation, 3) inhibitory tone, 4) depression, and 5) opioid reactivity. The main effects of these factors will be discussed first, followed by a discussion of how these factors are expected to interact to predict the development of anginal pain.

**Nociceptive input.** The physiological substrate underlying angina is myocardial ischemia. As such, the nociceptive input provoking the angina is the severity of the

ischemia. However, as discussed above, though when ischemic severity is below a certain threshold it does not seem to cause pain, ischemic severity does not reliably predict pain across individuals even when it is above a certain threshold. One of the possible reasons for this lack of correspondence between ischemic severity and anginal pain perception is that there are differences in visceral pain threshold across individuals.

Studies have shown that individuals with silent versus symptomatic ischemia have different pain thresholds. Indeed, using an ischemic tourniquet as a pain stimuli, studies demonstrated that silent ischemics tended to take longer to report pain (Procacci, Zoppi, Padeletti, & Maresca, 1976; Droste et al., 1986; Kardos et al., 1994). Studies using a cutaneous electrical or thermal pain threshold technique, a proxy for visceral pain threshold, also found a relationship to ischemic sensitivity (Procacci et al., 1976; Droste et al., 1986; Sheffield, Krittayaphong, Go, Christy, Biles, & Sheps, 1997; Sheps et al., 1999). The higher pain thresholds in silent ischemics might generalize to other areas as well. Pain tests in areas such as the toe, finger or dental pain thresholds, also showed that patients with silent ischemia seemed to have higher pain thresholds than patients with symptomatic ischemia (Pedersen, Pietersen, Madsen, Ballegaard, Meyer, & Trojaborg, 1989; Falcone et al., 1988).

However, this effect does not seem to be independent of some cognitive processing. For example, a study using electrical, thermal, and ischemic tests found that when stimuli were presented in sequential order (from less nociceptive to more nociceptive), pain thresholds were able to differentiate silent and symptomatic ischemia in patients. However, when stimuli were presented randomly, pain thresholds could not differentiate between the two groups (Glusman et al., 1996). This result suggests that psychological

factors such as stress and anticipation influence the perception of nociceptive stimuli and contribute to whether or not it is experienced as painful (Glusman et al., 1996). The following section describes the impact of cognitive factors on the interpretation of pain in more detail.

**Cognitive-sensory information.** The second component of the NMT of pain is cognitive-sensory information that influences the interpretation of a nociceptive stimulus (Melzack, 1999). The visual or other sensory inputs for visceral pain are less clear than those for somatic pain. For example, in somatic pain, one could expect that the visual input of stubbing one's toe would contribute to the interpretation of nociception in one's toe. If the nociception from the toe was paired with visual information that one's toe was not intact, the cognitive interpretation of this nociception would change dramatically. However, the absence of these visual cues are a hallmark of visceral pain such as angina.

The cognitive-sensory information related to anginal pain thus can be conceived of as a type of chest pain that the individual recognizes and identifies as anginal pain through memory (Melzack, 2001). As such, a memorable past experience of anginal pain would influence the interpretation of any nociceptive sensation from the myocardium or from a situation similar to that which produced the pain previously. Indeed, this previous experience of exertional angina would promote stress in anticipation of the next experience of exertion, which might make any nociceptive stimulus be perceived more quickly and as being of greater intensity (Glusman et al., 1996). In angina pectoris therefore, the memory of an episode of chest pain with anginal features (e.g., radiating to the left arm) which is provoked by physical exercise may be a cognitive cue to orient the sufferer to whether a current episode of angina is being experienced.

Indeed, research shows that individuals with a prior history of anginal pain are more likely to report angina in daily life 6 months post-MI (Ladwig, Röhl, Breithardt, & Borggrefe, 1999). Similarly, angina at post-operation predicts chronic chest pain at 6 months after coronary artery bypass surgery (Steegers, van de Luitgaarden, Noyez, Scheffer, & Wilder-Smith, 2007). The same result was found with experimental, as opposed to recalled, anginal pain (Arnold et al., 2009). Thus it seems like having a history of angina may modify the perception of future pain.

However, having these relationships raises other questions regarding the individual's sensitivity to pain stimuli. The next section discusses how there may be individual differences in the likelihood of being susceptible to various components of pain based on general neural inhibition.

**Inhibitory tone.** The next factor described in the NMT is inhibitory tone. The theory defines inhibitory tone as the “intrinsic neural inhibitory modulation inherent in all brain function” (Melzack, 1999, p. S125). This factor therefore refers to the individual's ability to inhibit the over-activation of responses to all the sensory and emotional stimuli inherent in daily life.

In terms of anginal pain, this factor can be operationalized as the likelihood individuals perceive and report a variety of vague excitatory sensations. Measures that relate to autonomic or somatic perception may provide valuable insight into how effectively individuals inhibit the perception of physical or other symptoms that may or may not have any actual significance for their health (Pennebaker, 1982). Such measures, such as the Autonomic Perception Questionnaire (APQ; Mandler, Mandler, &



Uviller, 1958), often correlate with hypochondriasis (Barsky & Wyshak, 1989) and general sensitivity to pain (Freedland et al., 1991, 1996).

This lower tendency to perceive and report symptoms may be related to silent myocardial ischemia (Barsky, Wyshak, & Klerman, 1990). According to the Neuromatrix Theory, this result would be explained by positing that individuals with higher tendencies to report symptoms are simply less capable of inhibiting any level of nociception. Though in the Neuromatrix Theory, inhibitory tone refers to a neural process in the CNS, the measure of symptom perception/inhibition speaks to the effects this neural inhibition is expected to produce.

**Tonic affective factors.** The next factor in the Neuromatrix Theory is similarly conceptualized as a neurological process that can be measured in its psychological epiphenomenon, affect. Affective factors have long been known to be important in cardiac pain (Heberden, 1772 as cited in Sylven, 1989). As described above, depression has been the most widely studied affective factor in anginal pain. The following section describes the research in this area in more focused detail.

***Angina and the development of depression.*** There is a bidirectional relationship between angina and depression, such that angina both predicts and is predicted by depression. This section describes the former of these relationships while the following section describes the latter.

Longitudinal studies have shown that patients with chest pain are at risk for psychological consequences (Robertson, Javed, Samani, & Khunti, 2008). This is true both for pain of cardiac and non-cardiac origin (Sheps, Creed, & Clouse, 2004). Retrospective studies have shown that individuals coming in for SPECT tests who

reported more angina over the prior 4 weeks had more angina, more history of revascularization, and more anxiety and depression, controlling for the amount of inducible ischemia on the stress test (Arnold et al., 2009).

Thus, there is a particular relationship between anginal pain and the development of psychological sequelae of angina. This relationship depicts the result of repeated episodic pain on affect and behavior. The following section describes this relationship in a different light, that of depression as a factor involved in the etiology of angina.

***Depression and the development of angina.*** Some researchers suggest that depression not only plays a causal role in the development of CAD in general, but of angina pectoris as well (Strike & Steptoe, 2002). Research supporting this theory has included longitudinal studies that showed that depression after MI predicted angina such that individuals with depression were 3 times more likely to experience pain as individuals with no depression, controlling for severity of CAD (Ladwig et al., 1999).

This study did not look at experimental angina, but angina recalled over time. However, another study examining experimental angina showed a similar effect. Indeed, people with depressive symptoms were shown to be more likely to perceive angina of longer duration and greater intensity than people without depressive symptoms, controlling for ischemic severity (Krittayaphong, Biles, Christy, & Sheps, 1996).

**CNS modulation.** According to the NMT, other CNS-related physiological systems aside from the sensory and nociceptive parts of the CNS operate to modulate the experience of pain. One component of this central modulatory system will be discussed below: the opioid/  $\beta$ -endorphin system. The opioid hypothesis has been present in angina

for a long time and evidence in its favor will be discussed below (Glazier et al., 1986; Sheps et al., 1988, 1991; Droste & Roskamm, 1989).

Several studies have shown a correlation between  $\beta$ -endorphin levels and pain perception (Droste et al., 1983; Light et al., 1991; Hikita, Etsuda, Takase, Satomura, Kurita, & Nakamura, 1998). Research has also demonstrated a relationship between resting  $\beta$ -endorphin levels and anginal pain, such that individuals with higher resting  $\beta$ -endorphin are more likely to be asymptomatic (Falcone et al., 1988). Further evidence of a relationship between anginal pain perception and  $\beta$ -endorphin levels comes from studies demonstrating how the administration of  $\beta$ -endorphin can counteract adenosine-provoked anginal chest pain (Sylvén, Eriksson, Sheps, & Maixner, 1996).

However, many studies have found no relationship between plasma  $\beta$ -endorphin levels and pain during ischemia (Weidinger, Hammerle, Sochor, Smetana, Frass, & Glogar, 1986; Glusman et al., 1996; Heller et al., 1987). Rather, these studies suggest that  $\beta$ -endorphin levels increase after mental and physical stress as part of the normal stress response, and have little impact on pain perception during ischemia (Marchant, Umachandran, Wilkinson, Medbak, Kopelman, & Timmis, 1994; Cantor, Shapiro, Eyal, Gueron, & Danon, 1990). Thus it is unclear whether opioid levels or opioid reactivity play a determining role in the perception of pain during ischemia. There is the added issue of peripheral  $\beta$ -endorphin being an uncertain measure of central  $\beta$ -endorphin, and of its being unable to cross the blood-brain barrier. Some thus believe it can have no direct effect on nociception, if nociception is controlled by the brain.

That being said, there seems to be a relationship between the opioid system and the perception of pain during ischemia (Sheps et al., 1995). However, it is likely that as a

main effect, opioid reactivity to stress just does not explain whether or not a given ischemic episode will be painful or not. That being said, it may play an important role as a modulator of, for example, the relationship between pain threshold and anginal pain perception. The following section describes which modulatory effects can be expected from the five factors described above based on the existing literature.

### **The interactions among components of the NMT**

Much research has focused on the main effects of the five factors described above on the experience of angina. However, the NMT predicts that not only will these factors produce main effects predicting the experience of pain, but also, and more importantly, there will be interactions among them that will predict pain more powerfully. In the case of silent versus symptomatic ischemia, this theory may help to explain why no single factor has yet to account for the occurrence of pain.

There are potentially dozens of interactions among the five factors described above, but the following section will be limited to those first-order interactions that are indicated given the literature and existing conceptual models. As such, we will discuss only the following interactions: the interaction of depression with opioid reactivity, symptom perception, and pain threshold; the interaction of history of angina with symptom perception; and the interaction of pain threshold with symptom perception and opioid reactivity.

**Interactions with depressive symptoms.** Depressive symptoms present with many physiological correlates. The following sections review the interactions between depressive symptoms and opioid modulation, symptom perception, and pain threshold. Most of the studies described below assess depressive symptoms using self-report

questionnaires of mood and somatic symptoms over the past week or two weeks. Cases where depressive symptoms were assessed differently will be highlighted.

***Interaction of depressive symptoms and opioid modulation.*** There is a relationship between depressive symptoms and the central nervous system. Indeed, some of the pathways relating visceral pain to the central nervous system overlap with those involved in the processing of psychological distress (Anand, Aziz, Willert, & van Oudenhove, 2007). For example, both clinical depression and certain pain syndromes are thought to be related to dysregulations in the serotonin system. These dysregulations include low levels of central serotonin, or disruptions in the serotonin receptors in the brain (Nordquist & Oreland, 2010). Research has shown that some pharmacologic antidepressant treatments targeting these neurochemical are also effective in decreasing complaints from certain pain syndromes (O'Malley et al., 1999; Crofford, 2008).

The opioid system has also been implicated in depressive symptoms (Light, Kothandapani, & Allen, 1998). Though it has often been suggested that the opioid system may be correlated to affect which affects pain directly (Sheps et al., 1988), the NMT would suggest more of a moderating relationship between the two. It is more informative to examine if those individuals who report more depressive symptoms and who also have lower  $\beta$ -endorphin reactivity to stress are more likely to report anginal pain.

The impact of such moderators may help explain some of the disparate findings for the relationship between depressive symptoms and angina, such that it seems to be both associated with higher levels of angina and with silent ischemia (see above). These differences may reflect genetic differences between individuals in stress-induced opioid

analgesia. Indeed, perhaps people who genetically have greater  $\beta$ -endorphin reactivity to stress display more silent ischemia if also high in depressive symptoms, whereas people with less  $\beta$ -endorphin reactivity to stress display an increase in anginal pain frequency or intensity.

There may, as such, be a quantitative difference in the effects of depressive symptoms in people with versus without high resting  $\beta$ -endorphin levels. The hypothesis therefore would be that individuals who have both 1) higher depressive symptoms and 2) lower  $\beta$ -endorphin reactivity would be particularly likely to report pain during ischemia.

***Interaction between depressive symptoms and symptom perception/inhibition.*** A further element which may moderate the relationship between depressive symptoms and pain perception during ischemia, may be the symptom perception/inhibition tendencies of the individual. For example, an individual who is high in depressive symptoms but who is not usually attentive to his or her bodily symptoms may be in fact less likely to perceive and report pain, whereas the opposite may be true for an individual high in depressive symptoms but low in symptom inhibition.

Indeed, it has been suggested that individuals experiencing higher levels of depressive symptoms are unable to get engaged in the experimental task and therefore report less sensitivity to pain (Dickens, McGowan, & Dale, 2003). Similarly, depressed individuals who display high levels of inhibition of symptoms may be less likely to have anginal pain during ischemia.

***Interaction between depressive symptoms and pain threshold.*** By a similar logic, the relationship between depressive symptoms and the perception of pain during angina may be influenced by the individual's pain threshold.

Pain threshold may be influenced by the presence of negative mood. For example, a study using emotion-induction (i.e., the creation of depressed mood by having participants read a series of sad statements aloud) showed that depressed mood led to increased ratings of pain severity on an acute pressure pain task in some individuals (Carter, McNeil, Vowles, Sorrell, Turk, Ries, & Hopko, 2002). However, the possibility of a moderating effect has not been assessed. In a clinical pain setting, it seems likely that those individuals who show both depressed mood and more sensitive pain thresholds may be particularly likely to perceive angina.

### **Interactions with pain threshold.**

***The interaction between pain threshold and symptom perception/inhibition.*** The relationship between pain threshold and anginal pain during ischemia may be moderated by some of the factors discussed above as well. Indeed, pain threshold assessed by a behavioral task, such as a thermal probe task, may be related to anginal pain perception in those individuals who are low in symptom inhibition, and not show this association in individuals who are high in symptom inhibition.

Symptom perception and inhibition correlates with psychological sensitivity to pain, as well as neuroticism and autonomic dysfunction (Freedland et al., 1991; Barsky et al., 1990). These factors may be potent moderators of the relationship between visceral pain threshold and anginal pain perception during ischemia.

***The interaction between pain threshold and opioid modulation.*** Pain thresholds do not operate in isolation in the determination of anginal pain during ischemia (Gitterman et al., 2009). The opioid system may play an important role such that those individuals who show strong  $\beta$ -endorphin reactivity may show a weaker association

between pain thresholds and angina. This response may operate as part of the acute stress produced analgesic response described above.

Indeed, increases in plasma  $\beta$ -endorphin after stress are significantly correlated with increases in thermal pain thresholds (Sheps et al., 1995). Thus it seems that the relationship between visceral pain threshold and anginal pain perception during ischemia may be moderated by the levels of plasma opioids.

### **History of angina.**

*The interaction between history of angina and symptom perception.* History of angina, in this model, represents a memory which serves a cognitive-sensory function leading an individual to interpret their present experience in light of this information. This would make these individuals much more likely to interpret any sensations from the myocardium, or even any situation involving exertion, as a trigger for anginal chest pain.

However, this relationship should be stronger in individuals who have a low level of inhibition of symptoms. Those individuals who have a high level of symptom inhibition should be less likely to be influenced by their prior experience of pain.

### **Other moderators of anginal pain**

The factors of the Neuromatrix Theory of pain are in reality compounds of multiple elements. The five factors described above, that is 1) visceral pain threshold, 2) history of angina, 3) symptom inhibition, 4) depressive affect, and 5) opioid modulation, are all elements that have been identified in the research on silent and symptomatic ischemia that map onto the five factors of the NMT. However, this section is devoted to some other variables that seem to be shown to influence the pain experience during ischemia.



These factors have been related to pain and will be included in the study presented below as covariates.

**Age.** Some studies suggest that the perception of pain during myocardial ischemia becomes blunted with age (Umachandran et al., 1991; but Ladwig et al., 1999).

**Sex.** Women report more intense and more frequent bodily symptoms than men (Barsky, Peekna, & Borus, 2001; Kimble et al., 2003). However, women have been demonstrated to be more prone to silent ischemia than men, including in the present sample (Forslund et al., 1998; Sheps et al., 2001). Indeed, this may reflect that there is a gender difference in the way that symptoms are reported, with women recalling more pain and being more willing to report pain, but men being more likely to report pain at stress or under certain circumstances (Pennebaker, 1982).

**History of hypertension.** Resting blood pressure is associated with the development of pain during exercise treadmill testing (Ditto et al., 2010; Bacon et al., 2006; Ditto, D'Antono, Dupuis, & Burelle, 2007; Go et al., 1997). Indeed, higher systolic blood pressure before exercise stress has been correlated with lower levels of angina (Go et al., 1997; Krittayaphong & Sheps, 1996). There is some support to suggest that patients with hypertension present a modified pain perception mechanism (France, 1999). Indeed, patients with hypertension may be more likely to experience silent myocardial events (Kannel, Dannenberg, & Abbott, 1985).

**History of diabetes.** History of diabetes may influence the perception of pain in patients with ischemic heart disease (Umachandran, Ranjadayalan, Ambepityia, Marchant, Kopelman, & Timmis, 1991; Ranjadayalan, Umachandran, Ambepityia, Kopelman, Mills, & Timmis, 1990).

**History of MI.** Pain perception may be affected by history of MI due to the tissue necrosis affecting the operation of the nociceptive pathways in the myocardium (Leach & Chester, 2010).

**Maximum ST-segment depression.** Maximum ST-segment depression will be used as a marker of ischemic severity, in order to control insofar as possible, for the nociceptive input due to ischemia (Bogaty et al., 1997).

### **Purpose of the present study**

This study aims to use Melzack's (1993) NMT of pain to understand the main effects of 1) nociceptive, 2) cognitive-perceptual, 3) inhibitory, 4) affective, and 5) opioid influences on the perception of anginal pain during ischemia. The study also examines whether certain interactions among these factors will be more predictive of anginal pain than the main effects alone.

### **Specific Aims & Hypotheses.**

Specific Aim I: To determine the relationship between anginal pain and the 5 factors of the NMT.

H1a: Anginal pain during exercise will be predicted by 1) lower pain threshold, 2) history of angina, 3) higher levels of symptom perception, 4) higher levels of depressive symptoms, and 5) lower  $\beta$ -endorphin reactivity.

Specific Aim II: To determine the relationship between anginal pain and the interactions between the 5 factors of the Neuromatrix theory.

H2a: Symptom perception, pain threshold, and  $\beta$ -endorphin reactivity will moderate the relationship between depression and exercise angina.

H2b: Symptom perception will moderate the relationship between history of angina and exercise angina.

H2c: Symptom perception and  $\beta$ -endorphin reactivity will moderate the relationship between pain threshold and exercise angina.

## **Methods**

The present study is a substudy of the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study. The methods of this study have been described in more detail previously (Goldberg et al., 1996; Kaufmann et al., 1998). Our study aims to investigate the multiple predictors of exercise-induced angina using the Neuromatrix Theory. The following section discusses the sections of the PIMI study methodology that are relevant to the present inquiry.

### **Participants**

Patients were eligible for the PIMI study if they had 1) either a positive angiogram ( $\geq 50\%$  narrowing of at least one major coronary artery) or previous MI, and 2) if they showed a positive ischemic response to an exercise treadmill test (ETT) while off anti-ischemic medications. Patients were excluded for the following: 1) pregnancy, 2) MI within three months of the ETT, 3) major cardiac surgeries, 4) unstable angina (i.e., anginal pain during rest or sleep) in the past month, 5) other serious illness or neurologic disease, 6) inability to discontinue medication for testing, and 7) abnormalities in the ECG which would interfere with the interpretation of the ambulatory ECG (AECG).

Patients were recruited from 4 sites: Henry Ford Hospital, Detroit, MI, St. Louis University Health Sciences Center, St. Louis, MO, University of Alabama at

Birmingham, Birmingham, AL, and University of Florida, Gainesville. Participants were recruited through participation in a previous protocol (Pepine et al., 1994), catheterization or exercise laboratories, or chart review. Consent of the attending physician was required to allow patients to participate. All participants provided informed consent.

## **Procedures**

The following discussion will be limited to the procedures of relevance to the present study. A fuller discussion of the PIMI methods is found in Kaufmann et al. (1998) and Goldberg et al. (1996). Participation consisted of an initial Qualifying Visit, followed by a Clinic Visit, as well as a 48-hour ambulatory ECG (AECG) monitoring time. The Qualifying Visit was used to determine whether the patient was medically eligible. If so, they were asked to return for the Clinic Visit after discontinuing medication for 48 hours.

The Clinic Visit was a half day of testing, consisting of a battery of psychological questionnaires (i.e., depressive symptoms, symptom perception, and history of angina), and a maximal bicycle exercise test, followed by radio ventricular imaging to detect ischemia. The bicycle exercise test followed a Bruce protocol. During this visit, patients also underwent pain threshold testing and blood draws at different points before, during, and after the bicycle test.

The present study examined a subset of the total 196 patients enrolled in the PIMI study. We included 175 of these patients, restricting the analyses to those patients who had confirmed ischemia on the bicycle test as assessed by ECG, AECG, or wall motion abnormalities. The patients were thus identified as experiencing true angina. The measurement of angina is discussed next.

## Measures

**Exercise-induced angina.** Silent versus symptomatic ischemia was assessed in a binary fashion. Anginal pain was determined as present or absent during the bicycle stress test. If the patient had ischemia indexed either through ECG, Holter monitoring during the bicycle test, or radio ventricular imaging they were included in the analyses. Ischemia during ECG was defined as a 1mm change in the ST-segment depression. Regional wall motion changes from the radio ventricular imaging were interpreted by a physician blinded to the patient's status as healthy or ischemic.

The bicycle test is a submaximal exercise test, however, it was used in the present analyses instead of the standard exercise treadmill test (ETT). To be eligible to participate in the study, the patients had to have ischemia on the standard ETT. Once this was ascertained, the patients proceeded to complete the experimental anginal task, which made use of the bicycle exercise test. The further advantage of the bicycle test is that it occurred after the administration of the battery of psychological questionnaires, and the baseline measures of pain threshold and blood markers. The use of the bicycle test allows us to examine the predictor of angina in this project.

**History of angina.** The measure of whether a person had a history of angina was taken from the results of the Rose Angina Questionnaire (RAQ; Rose, 1962) and coded as a binary measure (yes vs. no). The RAQ consists of a series of questions used to evaluate whether or not chest pain is likely to be of ischemic origin. It uses the traditional definition of angina as chest pain that "limits exertion, is situated over the sternum or in the left chest and left arm, and is relieved within 10 minutes by rest" (Rose, 1962; Fischbacher, Bhopal, Unwin, White, & Alberti, 2001). If the patient reported exertional

chest pain in the sternum or left arm that is relieved within 10 minutes when they stop or slow down on the RAQ, they were coded as having a history of angina (Rose, 1962).

**Depressive symptoms.** Depressive symptoms were measured using the Beck Depression Inventory (BDI; Beck, Steer, Garbin, 1988). The BDI is a series of 21 questions asking individuals to rate their mood over the past week. This questionnaire provides a continuous measure of depressive symptoms and was used to evaluate patient's affective state.

**Pain threshold.** Hot pain thresholds (HPT), a proxy for visceral pain thresholds, were obtained using the Marstock task (Fruhstorfer, Lindblom, & Schmidt, 1976; Sigurdsson & Maixner, 1994). Lower scores identify individuals as being more sensitive.

**Opioid modulation.** Patients underwent blood tests before, during, and after exercise stress testing. Baseline samples of  $\beta$ -endorphin levels were drawn after a 30-minute rest period. At peak exercise, samples were drawn again. Reactivity in  $\beta$ -endorphin levels was calculated by subtracting the baseline levels from the peak levels. All samples were analyzed in the core laboratory (Kaufmann et al., 1998).

**Symptom perception.** The modified Autonomic Perception Questionnaire (APQ; Mandler et al., 1958) was used to measure levels of symptom perception (Freedland et al., 1991, 1996). The APQ is a 21-item scale of the frequency with which autonomic symptoms are perceived when anxious. This measure provides an indication of the individual's tendency to perceive and report bodily symptoms. The modified version of the scale does not restrict the participant to their perceptions while anxious, and the items include some general or musculoskeletal items as well as autonomic function. This scale

provides an index of symptom perception; it was assumed that a tendency to perceive more bodily symptoms would be related to anginal pain during ischemia.

### **Statistical analyses**

Our hypotheses will be evaluated using a series of logistical regression models. First, a series of five main effects models will be constructed to evaluate whether each of the five factors described above predict the occurrence of angina at exercise independently. These models will be run first univariately, and then, including covariates in the first step. Second, a single model including all five independent factors in one block will determine whether their combined effects are predictive of exercise-angina than any factor considered alone. Finally, a series of six regression models will be built to evaluate whether the six planned interactions independently predict the occurrence of exercise-angina. All multivariate models will include age, sex, history of hypertension, history of diabetes, history of MI and maximum ST-segment depression (a measure of ischemic severity) as covariates because of their known relationship to anginal pain perception. Covariates were selected *a priori* based on literature described above. All analyses will be performed using SPSS version 14 (SPSS Inc., Chicago, IL).

**Power analysis.** We estimated the power for the above logistic regression analyses using the method described by Hsieh's (1989, p.797). There were 175 patients with ischemia on the bicycle test. Assuming a one-tailed test with  $\alpha=0.05$ , power of  $1-\beta=80$  per cent, and a target outcome (i.e., exercise-angina) prevalence of approximately 35%, the five independent main effects models are powered to detect an  $OR \geq 1.55$ . The full model including all five factors in one block, assuming inter-correlations between

variables of  $p^2 = 0.30$ , is powered to detect an  $OR \geq 1.70$ . The models detecting first-order interactions were also powered to detect an  $OR \geq 1.70$ .

## Results

### Demographics

The sample included 175 patients (26 women) all of whom developed ischemia during bicycle stress testing, as assessed by ECG, AECG or radionuclide testing. Of these 175 patients, 62 (35.4%) reported angina at exercise (Table 1). Age was separated into groups with the following percentages: 12 patients (6.9%) were 41 to 49 years old, 41 patients (23.4%) were 50-59 years old, 83 patients (47.4%) were between 60 and 69, and 39 patients (22.3%) were between 70 and 80 years old. Years of education was similarly split into groups with the following percentages: 36 (20.6%) had between 5 and 11 years of education, 52 (29.7%) had 12 years of education, 36 (20.6%) had between 13 and 15 years of education, and 51 (29.1%) had between 16 and 27 years of education. Most of the sample was White (153 patients, 78%).

Most of the sample lived with at least one other person (140 patients, 80.0%). Many participants held jobs, with 56 patients (32.0%) holding a full-time job and 16 patients (9.1%) holding a part-time job. Most of the sample was retired (86 people, 49.1%), and 17 patients reported work status of “other” (9.7%).

Many patients had a history of MI (67 patients, 38.3%) and 3 patients (1.7%) had documented coronary heart failure (CHF). Of the sample, 80 patients (45.7%) had documented hypertension, and 24 patients (13.7%) had documented diabetes mellitus. The sample’s mean BMI was 28.9 (SD=11.7) and the sample was predominantly White (153 patients, 87.4%).



### **The relationship between anginal pain and the 5 factors of the Neuromatrix theory**

Hypothesis 1 was that anginal pain (yes vs. no) during exercise would be predicted by 1) history of angina, 2) higher BDI score, 3) higher MAPQ score, 4) lower pain threshold, and 5) lower  $\beta$ -endorphin reactivity (see Figure 2 for the operationalization of the five factors of the Neuromatrix Theory). This hypothesis was evaluated using a series of hierarchical logistic regression models. The univariate models, without covariates, were constructed by entering the target variable in the first block. The multivariate models, including covariates, were constructed by entering the covariates in the first block and the target predictor variable in the second block.

**Cognitive-sensory factor: History of angina.** Binary logistic regression was used to analyse whether the memory of a previous episode of angina predicted exercise-angina (Table 2). Of the total sample, 75 patients (42.9%) reported a history of angina. The omnibus model for the univariate analysis was significant ( $p < 0.001$ ) with history of angina displaying a robust effect on anginal pain during exercise (OR=8.33, 95% CI=4.10-16.91). Of the 113 people who had silent ischemia during the bicycle test, 29 (25.7%) had a history of angina as assessed by the RAQ, whereas 46 people (74.2%) of the symptomatic group reported such a history.

The omnibus analysis of the full model, including age, sex, history of hypertension, history of diabetes, history of MI, and maximum ST-depression as covariates, was significant ( $p < 0.001$ ). Individuals with a history of angina were 8.59 times more likely to report pain during exercise than individuals with no history of pain (95% CI= 4.00-18.48). Having a history of angina thus is a good predictor of angina during exercise-stress testing.

**Affective factor: Depressive symptoms.** Hierarchical logistic regression was repeated to examine whether depression predicted angina during exercise (Table 3). The univariate model was marginally significant ( $p=0.093$ ). Within this model, there was a marginally significant relationship between depression and exercise-induced angina ( $OR=1.06$ ,  $95\% CI=0.99-1.11$ ), indicating that the odds of having exercise-angina increase by 6% for every one-point increase on the BDI. Individuals with silent ischemia had a slightly lower BDI score (mean=5.01,  $SD=5.19$ ) than individuals with pain (mean=6.48,  $SD=5.93$ ). The omnibus analysis for the full model, including covariates, was not significant ( $p=0.107$ ) suggesting that the effect of depressive symptoms on pain is not robust to covariates.

**Inhibitory tone factor: Symptom perception.** Hierarchical logistic regression showed that individuals who scored higher on the MAPQ, indicating greater sensitivity to somatic sensations, were not more likely to experience pain during exercise (Table 4). The omnibus univariate analysis, not including covariates, was not significant ( $p=0.845$ ). The silent ischemic mean (mean=93.77,  $SD=45.01$ ) was very close to that of the symptomatics (mean=95.29,  $SD=53.92$ ). The omnibus multivariate analysis including covariates, was also not significant ( $p=0.217$ ). As such, it seemed that general inhibitory tone, at least as measured by symptom perception, was not an independent predictor of pain during exercise.

**Nociceptive input: Hot pain threshold.** Hierarchical logistic regression was used to determine if hot pain threshold would provoke anginal pain in participants (Table 5). Without covariates, the relationship was not significant ( $p=0.503$ ). The omnibus test,

including covariates, was also not significant ( $p=0.347$ ). This analysis suggests that hot pain threshold does not independently predict angina during exercise.

**Opioid system:  $\beta$ -endorphin reactivity.** Finally,  $\beta$ -endorphin reactivity from rest to stress was examined for its impact on pain during exercise using the same analysis described above (Table 6). The omnibus model for the univariate analysis was not significant ( $p=0.660$ ). The omnibus test for the multivariate analysis, including covariates, was also not significant ( $p=0.152$ ). Patients with silent ischemia had a mean change in  $\beta$ -endorphin levels (mean=1.40, SD=3.50) that was not significantly different from that of symptomatics (mean=1.17, SD=2.61).

**Additive combination of the five factors.** A final model was constructed to examine the additive effects of all 5 predictors at once (Table 7). A logistic regression including all five factors in one block was significant at the  $p<0.001$  level. Of the five predictors, only history of angina significantly predicted exercise-angina (OR=7.914, 95% CI=3.61-17.35). The same was true of the omnibus model including all covariates. The model was significant ( $p<0.001$ ). However, of the 5 factors, history of angina was the only predictor of angina at exercise (OR=7.10, 95% CI=3.09-16.30).

**Summary.** Results from the single variable models and the full model suggest that history of angina is a robust predictor of exercise-angina, controlling for markers of severity of disease and severity of ischemia. Depressive symptoms also seem to be marginally predictive in a single univariate model, though the effect disappears when controlling for covariates or other factors. ST-segment depression was a significant predictor in all analyses, suggesting that the severity of ischemia plays an important role in the relationship between history of angina and exercise-angina, and depressive

symptoms and exercise-angina. All analyses were also repeated in the 145 participants with complete data for all the variables included in the full model. The results were not markedly different in terms of pattern of significance or effect sizes.

### **The relationship between anginal pain and the interactions between the 5 factors of the Neuromatrix theory**

The next main question we sought to assess was whether the five factors of the NMT would interact to moderate the relationship they had to exercise-angina. These analyses were calculated using hierarchical logistic regression. For the univariate analyses reported we entered the target factors in Block 1 (e.g., depression and hot pain threshold), and the interaction term in Block 2. For the multivariate analyses, we entered we entered all covariates (age, sex, history of diabetes, history of hypertension, history of MI, and maximum ST-segment depression) in Block 1, the target factors (e.g., depression and pain threshold) in Block 2, and the interaction term in Block 3. Results of all multivariate analyses are reported in Table 8.

**Interactions with depressive symptoms.** We hypothesised that depressive symptoms would interact with  $\beta$ -endorphin reactivity, symptom perception, and pain threshold to better predict exercise-angina than these factors alone.

***Interaction between the affective and opioid factors: Depressive symptoms and  $\beta$ -endorphins.*** A hierarchical logistic regression model was constructed to evaluate the predictive value of the interaction between depression and  $\beta$ -endorphins on the development of pain during exercise. The univariate model was not significant ( $p=0.404$ ), nor was the model controlling for covariates ( $p=0.221$ ).

***Interaction between the affective and general inhibition factors: Depressive symptoms and symptom perception.*** The same analysis was repeated for the interaction between depressive symptoms and symptom perception. Again, the interaction for both the univariate ( $p=0.296$ ) and the multivariate ( $p=0.203$ ) analyses were not significant.

***Interaction between the affective and nociceptive input factors: Depressive symptoms and pain threshold.*** The same analysis was used to evaluate the whether the interaction between depressive symptoms and hot pain threshold predicted angina during exercise. The omnibus model for the univariate analysis was significant ( $p=0.045$ ). The interaction term was marginally significant ( $p=0.054$ ) such that individuals who were more sensitive on the pain threshold task who also reported more depressive symptoms were most likely to have angina at exercise. Conversely, depressive symptoms did not affect anginal pain reporting during exercise in individuals who were not sensitive to pain during the hot pain threshold task (Figure 5). This model accounted for 5-6% of the variance in exercise-angina. This effect was not significant when controlling for covariates ( $p=0.134$ ).

**Interactions with history of angina.** We also hypothesised that symptom perception will moderate the relationship between history of angina and exercise angina.

***Interaction between the cognitive and inhibitory factors: History of angina and symptom perception.*** Hierarchical logistic regression was once again used to test the interaction between history of angina and symptom perception. The omnibus univariate and the model adjusting for covariates were significant (both  $p<0.001$ ). However, the interaction term was not significant in either the univariate ( $p=0.758$ ) or the multivariate ( $p=0.652$ ) analyses.

**Interactions with pain threshold.** We finally hypothesised that symptom perception and opioid reactivity will moderate the relationship between pain threshold and exercise angina.

***Interaction between the nociceptive and inhibitory factors: Pain threshold and symptom perception.*** The same analysis was conducted to evaluate the impact the interaction between pain threshold and symptom perception on exercise-angina. The final univariate ( $p=0.892$ ) and adjusted models ( $p=0.468$ ) were not significant.

***Interaction between the nociceptive and opioid factors: Pain threshold and  $\beta$ -endorphins.*** The interaction between pain threshold and  $\beta$ -endorphin reactivity on angina during exercise was also not significant for the univariate ( $p=0.911$ ) or the adjusted models ( $p=0.493$ ).

**Summary.** There was no evidence of a moderating effect between variables except for a marginally significant result for the interaction of depressive symptoms and hot pain threshold. Graphical analysis of the data suggests that in those individuals with lower pain thresholds, depressive symptoms might be a stronger predictor of anginal pain. Again all analyses were repeated in the 145 participants with complete data from the full model, with similar results.

## **Discussion**

Our study showed that history of pain is the most important component of the Neuromatrix Theory associated with anginal pain during ischemia. In the individual models, a history of angina was strongly predictive of pain in an acute experimental situation and there was a suggestion that depressive symptoms may be mildly predictive as well. The full model, containing all 5 factors, showed that history of angina was

predictive of pain above all other factors. The full model did not account for any more of the variance in predicting anginal pain than the single model including history of angina and covariates. The models examining the moderating effects of the factors were mostly not predictive of anginal pain in this situation. There was a marginal effect suggesting an interaction of depressive symptoms and thermal pain threshold, but the variance accounted for by this model was much lesser than that accounted for by history of angina. As such, this study suggests that models incorporating multiple predictors of pain, as suggested by the NMT, does not improve the predictive value of anginal pain in an acute experimental situation beyond the value of the most predictive factors.

The strongest finding of the study was that history of pain predicts acute experimental anginal pain. This result adds support to the notion advanced in the NMT of a 'pain signature'. Indeed, controlling for severity of ischemia as indexed by the ECG report as well as demographic and medical variables known to be associated with pain perception, history of angina was still a robust predictor of pain. Individuals with silent ischemia on the bicycle task thus do not seem to have had this 'pain signature' activated. It is possible that individuals endorsing a history of exertional chest pain were more likely to have experienced this recurrently to have developed a 'pain signature' through learning situations or proprioceptive cues that become pain triggers. As such, it seems that anginal pain may be learned through past painful experience.

Another explanation for the association between history of angina and exercise-angina is that individuals with histories of more severe ischemia may be more likely to have a history of pain, a suggestion which is supported by the involvement of ST-segment depression in our analyses. As such, there may be a change in the peripheral

nerve sensitivity to pain, akin to what has been suggested happens after MI (Leach & Chester, 2010).

The results regarding depressive symptoms seem to indicate a marginal effect on anginal pain in an experimental situation. One potential explanation for this marginal association is that it is possible that items on the depressive symptom scale reflecting a physiological burden of disease. Previous literature indicates that depression tends to be associated with recalled clinical pain (e.g., “Have you felt any angina in the past week or month?”; Arnold et al., 2009) which suggests that its relationship with exercise-angina may be mediated by other variables such as history of pain or symptom burden. As such, this result may have reflected ‘anginal symptom burden’ being predictive of pain in the experimental situation. This explanation must remain speculative, as the current study does not directly support this.

The results of the interaction analyses suggest another potential reason for the marginal association between depressive symptoms and anginal pain in this study. Perhaps only a subset of people, those who are sensitive to visceral nociception, display the effect. Indeed, it is possible that there is a genetic predisposition towards visceral pain sensitivity that leads to a correlation between depressive symptoms and angina, which is absent in those individuals who do not display this sensitivity. This clustering of symptoms would be in line with recent work on the interrelatedness of visceral pain pathways and emotional pain (Anand et al., 2009).

The NMT was developed based on a different pain syndrome, phantom limb pain, and is most often used to conceptualize chronic pain. However, it seems like its relevance is expanded to recurrent acute pains such as angina. Thus, the NMT provides



an interesting framework through which to consider different approaches to studying painful versus silent ischemia and to interpreting the results. That being said, most of the predictions from this theory did not display significant effects. Indeed, the study's first main hypothesis, which was that multiple factors would be more predictive than single ones, was not reflected in our results. The second main hypothesis, which was that interactions among predictors would be more powerful precursors to pain, also was not demonstrated.

Specifically, we did not find a significant effect for symptom reporting,  $\beta$ -endorphin reactivity, and hot pain threshold either as single predictors or as elements of a larger model. These main effects may have been absent from the current sample due to 1) analytic methods, 2) a weak effect (in the case of  $\beta$ -endorphins), and possibly 3) measurement error. Another issue could be in the process by which these factors affect pain. Indeed, there may be mediational effects of certain variables, rather than main effects, which were not tested in this study, due to lack of statistical power. Also, there could be secondary effects of some variables. For example, endorphin levels may affect the secondary cognitive processing of the pain, or the pain memory, rather than the immediate pain perception. Alternatively, the results may simply reflect that many of the factors described in the NMT do not show a statistically or clinically significant effect on experimental anginal pain.

### **Strengths and limitations**

The integration of a comprehensive range of variables represented a strength of this study. The PIMI study is the only study in the field of silent ischemia that allows the detailed examination of the effects of many different predictors of pain on a well-defined

measure of angina. The opportunity to take a multidimensional approach in this study represented one of the strengths of this dataset. Indeed, despite the fact that history of angina as a single predictor was as effective as history of angina in a multifactorial model, no single predictor of pain ever operates alone. A true understanding of the effects of one predictor may require examining it in the context of other, potentially important, variables.

Furthermore, many studies do not allow the differentiation between chest pain due to ischemia and chest pain due to other causes. The precise nature of the experimental pain, and the techniques used to assess the presence or absence of ischemia were particular strengths of this study. The use of experimentally (i.e., exercise) induced angina allowed us to identify which factors contribute to an acute anginal pain experience. Many other studies (e.g., Arnold et al., 2009), which showed a much larger effect size for depression on cardiac pain (i.e., OR between 2 and 3), used retrospective measures of angina rather than experimentally-induced pain, which may introduce bias relating to the recall of pain (Howren & Suls, 2011).

There are also several limitations to this study. This is a secondary analysis of a pre-existing dataset. As mentioned above, the strengths of this dataset are notable. However, given the nature of secondary analyses, we were not able to examine certain variables that may have been important or of interest. One such measure that was lacking was angiographically measured severity of CAD. Without this variable, it is difficult to ascertain how much severity of CAD contributed to the individuals reporting or not reporting angina. Furthermore, the use of the bicycle test for ischemia may have led to

submaximal exertion, such that it is possible that not all individuals received adequate ischemic nociception.

Also, since the present dataset was not collected with the NMT in mind, by using proxy measures for the five factors of the NMT, we could not evaluate combinations of variables appropriate to the theory that may have been more valid. As an example of the latter, our measure for symptom perception/inhibition was based on a single questionnaire measure. It would have been better to reduce a battery of questionnaires down to a symptom perception/inhibition factor and used that factor as a measure.

In addition, the NMT is vague in guiding specific hypotheses. The interaction effects that were tested were chosen based on conceptual theory and existing literature in the field of silent ischemia, but were not suggested as more important than other interactions according to the NMT. Inherent in the NMT is the suggestion that some of the interplay among these factors cannot be tested by current statistical methods, as relationships between these factors are suggested to be non-linear and involving multiple higher-order interactions. A related issue is the computation of numerous bivariate interactions. Though the number was restricted to those supported by the literature, there is a risk of increased Type I error due to the many analyses conducted.

In addition, the NMT is a theory of how inputs from the periphery are translated into “pain signatures” by neural circuitry, which are then interpreted and acted upon by other areas of the brain. This study did not examine any of the neurological factors that are postulated to underlie pain perception. There is evidence to support the involvement of a widespread network of circuits in the brain that influence cardiac pain perception. There is input from the periphery, which then becomes integrated with inputs from the

basal ganglia, the limbic system, and the prefrontal cortex, which are all activated in angina during myocardial ischemia (Sylvén, 1997). It is interesting to note that the sensory cortex does not show the same level of activation in this disorder. During silent ischemia, the same parts of the brain are involved, with the prefrontal cortex being involved to a lesser degree (Sylvén, 1997). The interpretation of these data is unclear but seems to suggest that the psychological factors, including interpretation of sensations, may be what drives the difference between silent and symptomatic ischemia.

Thus, additional measures that would have been informative outside of what was available as part of this secondary data analysis include: 1) angiographic severity of disease, 2) cardiac ischemic pain threshold, 3) neural pain inhibition by way of neuroimaging, 4) tendency to interpret pain as clinically significant, 5) central opioid pain modulation. These variables would have strengthened the measures of the five factors of the NMT and would have strengthened the covariates.

### **Implications of the present findings**

Clinically, it is important for physicians to be able to identify individuals who are at risk of silent ischemia. An individual with many risk factors for CAD (i.e., smoking, obesity, family history of cardiac disease) should be tested very carefully despite a lack of chest pain symptoms. It seems like the best predictor for exertional-angina is a history of angina. Therefore it seems like preventive efforts have to include education about the lack of symptoms that can accompany the development of CAD. Patients have to know that in many cases, they cannot expect to have pain as a warning signal, and should be encouraged to monitor their cardiac health closely with their physicians.

Another clinical implication suggested by this study relates to the possible overlap between depressive symptoms and anginal symptom burden in this population. It is possible that some of the depressive symptoms are either directly caused by or overlapping with disease symptom burden. As such, when treating anginal symptom burden, it may be important to examine what role depressive symptoms play. Some questions to consider include, for example, whether depressive symptoms exacerbate disease symptom burden? Does the treatment of depressive symptoms improve disease symptom burden as well? If one treats anginal pain, should one also treat the accompanying emotional reaction? Such work would provide not only theoretical insight into the mechanisms of silent versus symptomatic ischemia, but would also be of considerable clinical significance in determining which patients may suffer from too much, or from too little, anginal chest pain.

## **Conclusion**

The application of the NMT to the problem of silent versus symptomatic ischemia did not identify more triggers of cardiac pain. This work identified having a history of angina as being the factor which was most likely to predict acute anginal chest pain. Depressive symptoms also seemed to play a role in the perception of pain in this population. Ultimately, knowledge of these factors can be helpful in identifying who is at risk of experiencing too much versus too little pain during ischemia, and their clinical treatment can be modified accordingly.

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**Tables and Graphs**

Figure 1. Types of chest pain.

	<b>Ischemia</b>	<b>No ischemia</b>
<b>Pain</b>	Angina	Non-cardiac chest pain
<b>No pain</b>	Silent ischemia	Normal healthy heart

Figure 2. Operationalization of the NMT factors.

<b>Neuromatrix Theory of Pain (Melzack, 1993)</b>	
1) Nociceptive input	Ischemia, Pain threshold
2) Cognitive-sensory input	History of angina
3) Inhibitory tone	Symptom perception
4) Cognitive and affective factors	Depression
5) ANS, neuroendocrine, opioid systems	HRV (sympatho-vagal tone), $\beta$ -endorphins

Figure 3. Gate-Control Theory (figure from Melzack, 1993)

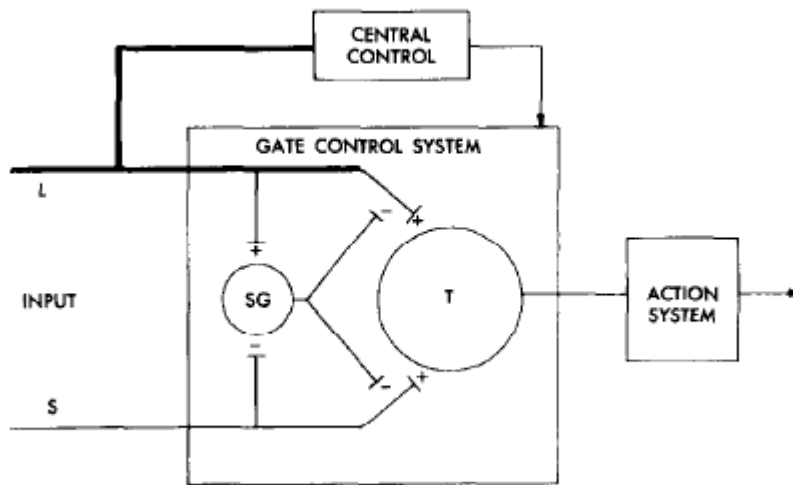




Figure 4. Neuromatrix Theory (figure from Melzack, 1993). S = sensory-discriminative; A = affective-emotional; E = evaluative-cognitive. S, A, and E refer to three domains of pain. This figure describes the interplay of factors contributing to the pain experience.

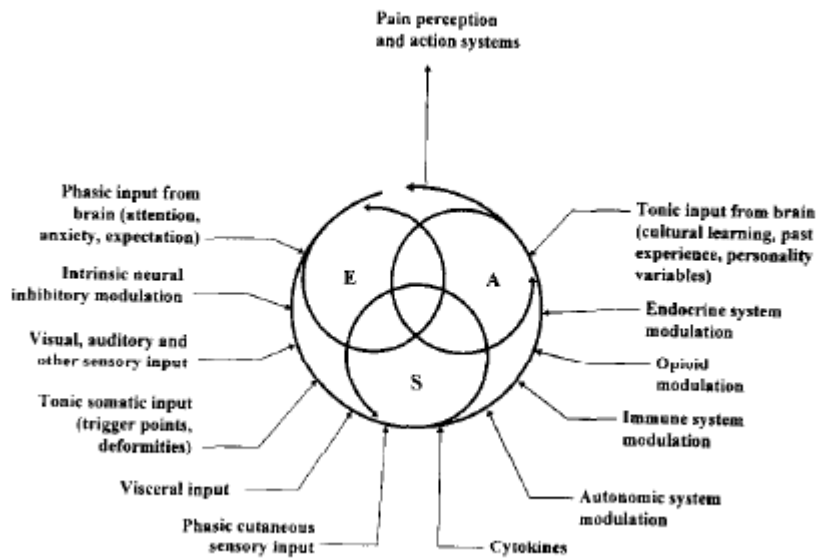


Figure 5. Interaction between depression and hot pain threshold.

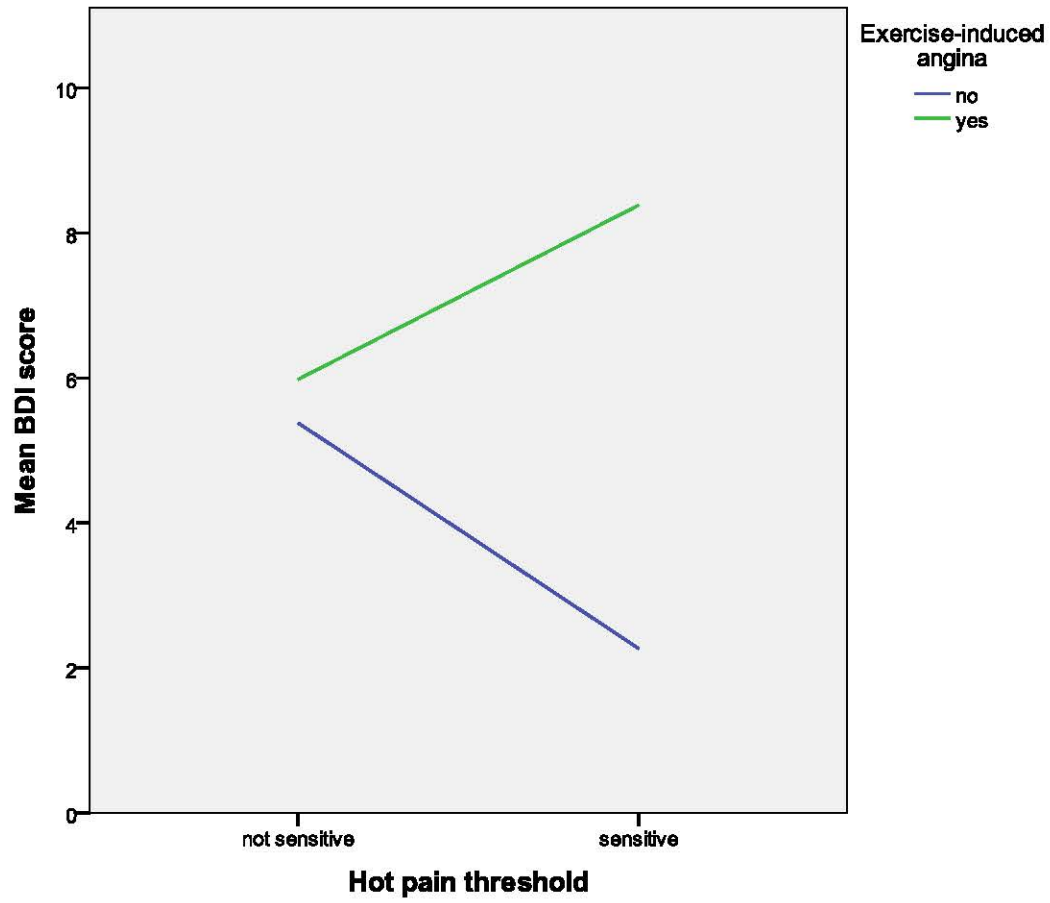


Table 1. Patient demographics split by silent versus symptomatic ischemia.

N=175	Silent ischemia N (%) N=113	Symptomatic ischemia N (%) N=62	p-value
Age			NS
4	9 (8.0)	3 (4.8)	
5	26 (23.0)	15 (24.2)	
6	57 (50.4)	26 (41.9)	
7	21 (18.6)	18 (29.0)	
Sex			NS
Men	99 (87.6)	50 (80.6)	
Women	14 (12.4)	12 (19.4)	
Years of education			NS
5 and 11 years	19 (16.8)	17 (27.4)	
12 years	33 (29.2)	19 (30.6)	
13 and 15 years	24 (21.2)	12 (19.4)	
16 and 27 years	37 (32.7)	14 (22.6)	
Living alone	16 (14.2)	19 (29.7)	0.009
Working			NS
full-time	38 (33.6)	18 (29.0)	
part-time	11 (9.7)	5 (8.1)	
Retired	53 (46.9)	33 (53.2)	
'other'	11 (9.7)	6 (9.7)	
History of MI	44 (38.9)	23 (37.1)	NS
History of CHD	3 (2.7)	62 (100.0)	NS
History of hypertension	49 (43.4)	31 (50.0)	NS
History of diabetes	17 (15.0)	7 (11.3)	NS
BMI - mean (SD)	29.7 (14.3)	27.5 (3.8)	NS
Race (White)	97 (85.8)	56 (90.3)	NS

Table 2. The relationship between history of angina and exercise-angina.

	N	B	S.E	OR	95% CI	<i>p</i>
<b>Univariate model†</b>	175					<0.001
History of angina (y/ n)		2.120	0.361	8.328	4.10-16.91	<0.001
<b>Multivariate model‡</b>	165					<0.001
Sex		-0.225	0.529	.799	0.28-2.26	0.671
Age		0.153	0.232	1.166	0.74-1.84	0.508
History of hypertension		0.058	0.388	1.060	0.50-2.27	0.881
History of diabetes		0.487	0.573	1.628	0.53-5.01	0.395
History of MI		-0.128	0.399	0.880	0.40-1.92	0.747
Maximum ST- segment depression		0.359	0.196	1.432	0.98-2.10	0.067
History of angina (y/ n)		2.151	0.390	8.587	4.00-18.48	<0.001

†  $R^2 = 0.20$  (Cox & Snell), 0.28 (Nagelkerke)‡  $R^2 = 0.23$  (Cox & Snell), 0.32 (Nagelkerke)

Table 3. The relationship between depressive symptoms and exercise-angina.

	N	B	S.E	OR	95% CI	<i>p</i>
<b>Univariate model†</b>	175					0.093
BDI score		0.048	0.029	1.049	0.99-1.11	0.097
<b>Multivariate model‡</b>	165					0.107
Sex		-0.539	0.483	0.583	0.23-1.50	0.264
Age		0.221	0.216	1.247	0.82-1.90	0.305
History of hypertension		-0.223	0.342	0.800	0.41-1.56	0.514
History of diabetes		0.575	0.519	1.777	0.64-4.91	0.268
History of MI		-0.029	0.357	0.972	0.48-1.96	0.936
Maximum ST-segment depression		0.360	0.173	1.434	1.02-2.01	0.037
BDI score		0.054	0.030	1.055	0.99-1.12	0.078

†  $R^2 = 0.02$  (Cox & Snell), 0.02 (Nagelkerke)‡  $R^2 = 0.07$  (Cox & Snell), 0.10 (Nagelkerke)

Table 4. The relationship between symptom perception/ inhibition and exercise-angina.

	N	B	S.E	OR	95% CI	<i>p</i>
<b>Univariate model†</b>	169					0.845
MAPQ score		0.001	0.003	1.001	0.99-1.01	0.845
<b>Multivariate model‡</b>	159					0.217
Sex		-0.859	0.482	0.423	0.17-1.09	0.075
Age		0.144	0.218	1.155	0.75-1.77	0.509
History of hypertension		-0.137	0.351	0.872	0.44-1.74	0.696
History of diabetes		0.485	0.521	1.624	0.59-4.51	0.352
History of MI		0.020	0.363	1.021	0.50-2.08	0.955
Maximum ST-segment depression		0.357	0.175	1.429	1.01-2.02	0.042
MAPQ score		0.003	0.004	1.003	1.00-1.01	0.480

†  $R^2 = 0.00$  (Cox & Snell), 0.00 (Nagelkerke)

‡  $R^2 = 0.06$  (Cox & Snell), 0.08 (Nagelkerke)

Table 5. The relationship between hot pain threshold and exercise-angina.

	N	B	S.E	OR	95% CI	<i>p</i>
<b>Univariate model†</b>	169					0.503
HPT		-0.025	0.037	0.975	0.91-1.05	0.502
<b>Multivariate model‡</b>	161					0.347
Sex		-0.579	0.492	0.561	0.21-1.47	0.240
Age		0.155	0.216	1.168	0.77-1.78	0.472
History of hypertension		-0.164	0.342	0.849	0.43-1.66	0.631
History of diabetes		0.317	0.538	1.373	0.48-3.94	0.556
History of MI		-0.069	0.356	0.933	0.47-1.87	0.846
Maximum ST-segment depression		0.346	0.171	1.413	1.01-1.97	0.043
HPT		-0.016	0.042	0.984	0.91-1.07	0.704

†  $R^2 = 0.00$  (Cox & Snell), 0.00 (Nagelkerke)‡  $R^2 = 0.05$  (Cox & Snell), 0.06 (Nagelkerke)

Table 6. The relationship between  $\beta$ -endorphin reactivity and exercise-angina.

	N	B	S.E	OR	95% CI	<i>p</i>
<b>Univariate model†</b>	161					0.660
$\beta$ -endorphin reactivity		-0.023	0.052	0.977	0.88-1.08	0.661
<b>Multivariate model‡</b>	152					0.132
Sex		-0.801	0.483	0.449	0.17-1.16	0.098
Age		0.188	0.223	1.207	0.78-1.87	0.399
History of hypertension		-0.323	0.352	0.723	0.36-1.44	0.359
History of diabetes		0.590	0.522	1.805	0.65-5.02	0.258
History of MI		-0.123	0.371	0.884	0.43-1.83	0.739
Maximum ST-segment depression		0.389	0.179	1.476	1.04-2.10	0.030
$\beta$ -endorphin reactivity		-0.051	0.055	0.950	0.85-1.06	0.356

†  $R^2 = 0.00$  (Cox & Snell), 0.00 (Nagelkerke)‡  $R^2 = 0.07$  (Cox & Snell), 0.09 (Nagelkerke)



Table 7. The full model relating all five factors to exercise-angina.

	N	B	S.E	OR	95% CI	P
<b>Full model – no covariates†</b>	151					<0.001
History of angina		2.069	0.401	7.914	3.61-17.35	<0.001
BDI score		0.049	0.037	1.050	0.98-1.13	0.184
MAPQ score		-0.003	0.004	0.997	0.99-1.01	0.520
HPT		-0.038	0.046	0.962	0.88-1.05	0.403
β-endorphin reactivity		-0.027	0.059	0.973	0.87-1.09	0.649
<b>Full model – including covariates‡</b>	145					<0.001
Sex		-0.336	0.604	0.715	0.22-2.34	0.578
Age		0.151	0.258	1.163	0.70-1.93	0.560
History of hypertension		0.073	0.417	1.076	0.48-2.44	0.861
History of diabetes		0.320	0.611	1.377	0.42-4.56	0.600
History of MI		0.009	0.424	1.009	0.44-2.31	0.983
Maximum ST-segment depression		0.377	0.208	1.458	0.98-2.18	0.066
History of angina		1.960	0.424	7.098	3.09-16.30	<0.001
BDI score		0.042	0.039	1.042	0.97-1.13	0.287
MAPQ score		0.000	0.005	1.000	0.99-1.01	0.943
HPT		-0.016	0.051	0.984	0.89-1.09	0.758
β-endorphin reactivity		-0.045	0.061	0.956	0.85-1.08	0.460

†  $R^2 = 0.20$  (Cox & Snell), 0.28 (Nagelkerke)‡  $R^2 = 0.22$  (Cox & Snell), 0.31 (Nagelkerke)

Table 8. Interactions including covariates.

	N	B	S.E	OR	95% CI	P
<b>Depression X</b>						
1) B-endorphins	153	-.002	.009	.998	.98-1.02	0.848
2) Symptom perception	159	.001	.001	1.001	1.00-1.00	0.360
3) Hot pain threshold	161	-.017	.009	.983	.97-1.00	0.071
<b>History of angina X</b>						
1) Symptom perception*	159	.004	.009	1.004	.99-1.02	0.652
<b>Hot pain threshold X</b>						
1) Symptom perception	155	-.001	.001	.999	1.00-1.00	0.415
2) B-endorphins	149	-.008	.014	0.992	.97-1.02	0.600

\*Model  $p < 0.05$